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March 10, 1998

C.W. Jameson, Ph.D.
NTP Report on Carcinogens
MD EC-14
P.O. Box 12233
Reser Triangle Park, NC 27709

Dear Dr. Jameson:

In its last bulletin, the National Toxicology Program has placed on its agenda for further discussion the possibility that the consumption of alcoholic beverages should be listed as a carcinogenic. Presumably, the items for discussion would relate to reports linking alcohol consumption to cancers of 1) the upper respiratory tract, 2) the esophagus, 3) the liver and 4) the female breast. I have been requested by representatives of the alcohol beverage industry to examine the literature regarding the putative association between alcohol intake and the development of various cancers and to communicate my impressions.

I am the Gonzalo E. Aponte Professor of Pathology and Chairman of the Department of Pathology, Anatomy and Cell Biology at Jefferson Medical College of Thomas Jefferson University, Philadelphia. I also serve as Physician-in-Chief for Pathology at Thomas Jefferson University Hospital. My enduring interests in human and experimental studies of the effects of alcohol are well known, and I have been continuously funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) for over 30 years. In this context, I am the principal investigator and scientific director of a NIAAA-funded Alcohol Research Center, the principal investigator of a grant entitled "The Effects of Alcohol on Subcellular Organelles of the Liver", for which I have recently received notification of a MERIT award, and the principle investigator of a training grant in alcohol studies. I have served three terms as a full time member of initial review groups (study sections) of NIAAA and have been chairman of several special review groups for NIH. In addition to publishing over 200 papers related to alcohol research, I have also edited two books for the Annals of the New York Academy of Sciences, namely "Alcohol and the Cell" and "Molecular and Cellular Mechanisms of Alcohol and Anesthetics." In the context of the issues to be discussed, I am enclosing a reprint of a recent paper that I authored (Rubin, E., The Questionable Link Between Alcohol Intake and Cancer, Clin Chim Acta:143-148, 1996).

The postulated link between alcohol consumption and cancer of any organ is based upon epidemiological studies that claim an association. Philosophically, if one wishes to take issue with such conclusions, it is indeed difficult to prove the negative, i.e.,

no weak association. Nevertheless, the burden of proof should be on those who claim an effect of alcohol. There is a general agreement that alcohol administration to experimental animals has failed to produce any cancer and that alcohol is not a mutagen in a variety of assays, including the Ames test, sister chromatid exchange, unscheduled DNA synthesis, etc. In evaluating the epidemiologic data, the following questions come to mind.

1. Is the association between the intake of alcoholic beverages and any particular cancer valid? In other words can the association be accounted for by confounders, such as selection bias, inappropriate controls, or environmental factors such as diet, the intake of other drugs, socioeconomic status, etc.? It is incorrect to assume a priori that the only differences between abstainers, moderate drinkers and heavy consumers of alcohol relate only to their ethanol intake. There are probably many other lifestyle factors that characterize each of these groups.
2. If the association between alcohol and cancer is valid, does it apply to moderate drinking or heavy alcohol consumption? In this context, are increases in the odds ratio or relative risk derived only by mathematical extrapolations or do they represent actual data?
3. If the association is valid, does it indicate a cause and effect relationship? The intelligent application of the Hill Criteria can be helpful. These include (among others) strength of the association, consistency, specificity, biologic gradient (dose-response), and biologic plausibility. It is not mandatory that a valid epidemiological study satisfy all these criteria, nor does adherence to them guarantee that the hypothesis derived from the data is necessarily true. Nevertheless, they are useful guidelines.

I will discuss each of these questions in the context of individual cancers that have been attributed by some to the intake of alcoholic beverages.

Cancers of the Upper Respiratory Tract

It has been suggested in a number of publications that alcohol intake leads to a substantially increased risk of oropharyngeal cancer and laryngeal cancer. Intuitively, an increased risk for laryngeal cancer is difficult to explain, since that tissue does not ordinarily come into contact with alcohol. In any event, both oropharyngeal and laryngeal cancers are predominantly diseases of smokers, and it has been difficult to find many heavy alcohol consumers who do not also smoke. Therefore, the statistical data for these diseases are derived principally from smokers and are adjusted mathematically by logistic regressions and other methods to arrive at an increased odds ratio. Even using such adjustments, the literature remains contradictory, and most studies demonstrate an effect only at higher levels of alcohol consumption. Considering the fact that many

studies have linked cancers of the upper respiratory tract to low levels of fruits, vegetables, vitamins, minerals and micronutrients in the diet, the failure to control for dietary confounding in alcohol abusers remains a problem.

Esophageal Cancer

A number of studies have reported an increase in cancer of the esophagus associated with alcohol consumption. However, the data for moderate alcohol consumption are weak and inconsistent. The statistics for heavy alcohol intake are more persuasive. However, it must be pointed out that esophageal cancer is a tumor that is unusually sensitive to environmental factors, most of which are unknown. For example, there is a large esophageal cancer belt that extends from the Caspian littoral to northeastern China, in which the prevalence of cancer of the esophagus is manyfold greater than that in western countries. In many of these areas, the populations do not smoke or drink, and it has been postulated that dietary influences or unknown toxic materials in the environment may be responsible. Thus, lifestyle differences and dietary factors cannot be excluded from consideration among alcohol abusers. Moreover, most of these studies relating alcohol consumption to cancer of the esophagus do not provide histologic data regarding cell type. This may be of particular importance, since the incidence of adenocarcinoma of the esophagus has been increasing rapidly in recent years and now comprises about half of all esophageal cancers in the United States. Adenocarcinoma of the esophagus arises in a metaplastic epithelium termed Barrett esophagus, which is a direct result of acid reflux from the stomach. Similarly, the incidence of squamous carcinoma of the esophagus is increased by epithelial injury secondary to acid reflux. It has been amply documented that alcohol consumption leads to relaxation of the lower esophageal sphincter and thereby results in acid reflux. Thus, this effect alone may be responsible for the reported increased incidence of esophageal cancer in heavy alcohol consumers.

Primary Hepatocellular Carcinoma

A number of papers in the literature have proposed that alcohol consumption is associated with an elevated risk of liver cancer. It is important to note that with the exception of a rare variant, termed fibrolamellar hepatocellular carcinoma, almost all cases of liver cancer arise in the setting of chronic hepatitis or cirrhosis. Since moderate drinking produces neither of these lesions, it can safely be assumed that it is in no way related to the development of liver cancer. Thus, any association is, almost by definition, restricted to chronic alcohol abuse.

The principal causes of liver cancer worldwide are infections with the viruses of hepatitis B (HBV) and hepatitis C (HCV). For reasons unknown, chronic alcoholics display a substantially higher prevalence of these infections than does the general population. Most of the studies relating alcohol to liver cancer do not adequately control for both of these infections. Some of the studies that have addressed this issue in HBV-negative patients do not account for integration of HBV in the genome. Others that record anti-HCV do not comment on the presence or absence of HCV RNA. Moreover,

it is generally accepted that alcohol consumption has a particularly deleterious effect on the course of chronic hepatitis C. In fact, persons suffering from that disease are now recommended to consume no more than one drink a day or, even better, entirely abstain from alcoholic beverages.

Hepatic iron overload, as in hereditary hemochromatosis, is associated with a greatly increased risk of liver cancer. The fact that cirrhosis results in increased hepatic iron (and even secondary hemochromatosis) should be considered a possible risk factor. It is true that the cirrhotic process itself, independent of viruses or other conditions, e.g. hemochromatosis, alpha-1-antitrypsin deficiency, porphyria, etc., may lead to increased turnover of hepatocytes and, thereby, increase the risk of primary hepatocellular carcinoma. However, in the case of chronic alcoholism, such an event appears to be distinctly uncommon.

Breast Cancer

A substantial amount of publicity has recently centered on reports of a link between alcohol consumption and female breast cancer. The studies of this topic have been inconsistent, and even those who claim an effect of alcohol have demonstrated only a weakly increased risk. Although publication of such small risks has been justified on the basis of the high prevalence of breast cancer, the possibility of confounding remains real. In 1994, a critical review by Roth et al, identified 38 case-control studies of alcohol and breast cancer. They pointed out that an analysis of five major review articles in the previous five years had concluded that "the present literature provides little reliable evidence for any causal association at mild or moderate levels of consumption." Roth, et al found that a significant association between the consumption of alcoholic beverages and breast cancer had rarely been reported in studies using community-based controls rather than hospital-based controls. In a paper that appeared in JAMA in February 1998, Smith-Warner et al describe a pooled analysis of cohort studies, in which a nonparametric regression curve supposedly shows that alcohol consumption is associated with a linear increase in breast cancer incidence, even at low levels of consumption. However, no significant increase is actually reported at levels below 30 grams of ethanol a day, which is twice the amount recommended by many for alcohol intake by women. Even at intakes of 30 to 60 grams of ethanol a day, the increase in risk from the pooled data is only 1.4, and perversely decreases to 1.3 at intakes greater than 60 grams a day. Thus, it is inappropriate to incriminate moderate alcohol consumption by women as a risk factor in the development of breast cancer. At higher levels of consumption, which may be termed alcohol abuse, there are many hormonal and dietary factors that may confound the issue, especially when confronted with minimal changes in the odds ratio.

In summary, the answers to the questions listed above do not permit labeling alcoholic beverages as carcinogens. At all sites, it is questionable whether moderate alcohol intake can be incriminated as a cause of cancer. Heavy alcohol consumption is associated with many possible confounders, although it cannot be ruled out that indirect effects produced by ethanol abuse may play a role. In this context, we do not label fat as

a carcinogen simply because high fat diets have been epidemiologically associated with cancers of the breast and colon. In the case of alcohol abuse and cancer, important Hill Criteria have not been met. The strengths of the associations remain weak, and the results of many studies are inconsistent. A dose-effect relationship is elusive, and if present seems to operate only at levels consistent with alcohol abuse. The biological plausibility is questionable, in view of the lack of molecular similarity of ethanol to known carcinogens, its failure to produce experimental cancers, and its lack of mutagenicity.

I have devoted many years to demonstrating the harmful effects of excessive alcohol consumption, and have never written on its beneficial effects. However, I do not believe that alcohol should be indicted as a carcinogen on the basis of the published literature. One may adopt the view that when dealing with common malignancies such as breast cancer, it is better to be safe than sorry. Yet there is strong evidence that moderate alcohol consumption actually prolongs life, and it is, therefore, a disservice to suggest that it is carcinogenic without more persuasive data. I will be pleased to support this position in greater detail should the committee consider it desirable.

Sincerely,

A handwritten signature in cursive script that reads "Emanuel Rubin".

Emanuel Rubin, M.D.

Attachment

The following journal article was attached to Emmanuel Rubin's comments. Due to copyright infringement laws we cannot display it. We have listed the citation for your information.

National Toxicology Program
Report on Carcinogens Group

Rubin E. 1996. The questionable link between alcohol intake and cancer. *Clinica Chimica Acta* 246:143-148.